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10/577,912	09/13/2006	Piero Del Soldato	026220-00082	6903

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EXAMINER	
HAVLIN, ROBERT H	

ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/577,912	DEL SOLDATO ET AL.	
	Examiner	Art Unit	
	ROBERT HAVLIN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above claim(s) *2-35, 37-56, 60-79, 81-90, 92-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,36,57-59 and 80* is/are rejected.

7)☒ Claim(s) *91* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/24/06 and 5/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims: Claims 1-98 are currently pending.

Priority: This application is a 371 of PCT/EP04/13683 (12/01/2004) and claims foreign priority to EUROPEAN PATENT OFFICE (EPO) 03104484.5 (12/02/2003).

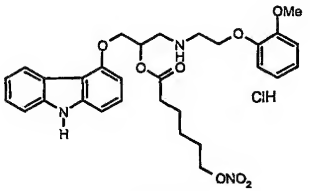
IDS: The IDS dated 5/24/06 and 5/1/06 were considered.

Election/Restrictions

1. Applicant's election with traverse of Group II (claims 1-94 and 98, in part, drawn to a product where R1 is IIb) in the reply filed on 6/5/09 is acknowledged. The traversal is on the ground(s) that the groups I-XXIV relate to a single inventive concept sharing a common technical feature not disclosed in the prior art. This is not found persuasive because the common technical feature shared is that of formula II which is known in the art as stated in the prior office action. In addition, other prior art such as US 4,288,452 as well as those cited in the following rejection teach compounds which share the same common structural element of formula II.

The requirement is still deemed proper and is therefore made FINAL.

Applicant also elected the species (allegedly reading on claims 1, 36, 57-59, 80, and 91) of compound (110) also described in example 7 having the following structure:



(110)

As detailed in the following rejections, the generic claim encompassing the elected species was not found patentable. Therefore, the provisional election of species is given effect, the examination is restricted to the elected species only, and claims not reading on the elected species are held withdrawn. Accordingly, claims 2-35, 37-56, 60-79, 81-90, 92-98 are hereby withdrawn.

Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection through amendment, the amended Markush-type claim will be reexamined to the extent necessary to determine patentability of the Markush-type claim. See MPEP § 803.02.

Claim Objections

2. Claims 1 and 36 are objected to because of the following informalities: the claim does not end with a period. Appropriate correction is required.

3. Claim 91 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claim 91 has not been further treated on the merits.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

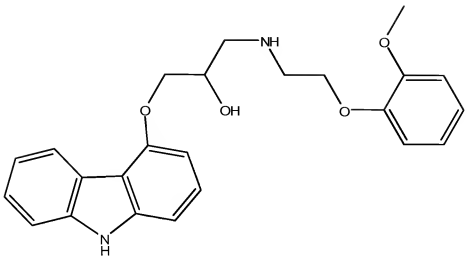
5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1, 36, 57-59, and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,932,538 ('538).

The instant claims read on nitrosating modifications to antihypertension compounds and specificially Carvedilol.

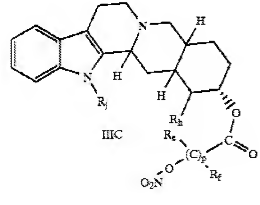
Carvedilol has the following structure:



The elected species in the instant application is the 6-nitrosated hexanoic ester of carvedilol.

1. Determining the scope and contents of the prior art.

'538 teaches a particular type of modification of known alpha-adrenergic receptor antagonists. Specifically, the reference teaches chemical modifications that result in the release of nitric oxide. The reference teaches in col 19 an example of nitrosating an alpha-adrenergic receptor antagonist by esterifying the available hydroxyl group of the compound to give the following structure:



. The definitions of Re, Rf, and p include the hexanoic ester.

The reference also teaches carvedilol is an alpha-adrenergic receptor antagonist that can be modified in the same way to produce a nitrosated alpha-adrenergic receptor antagonist that releases nitric oxide.

2. Ascertaining the differences between the prior art and the claims at issue.

The difference between the prior art and the claims is the particular selection of the hexanoic ester of carvedilol.

3. Resolving the level of ordinary skill in the pertinent art.

One of ordinary skill in the art routinely makes modifications of known pharmaceutical agents to enhance or improve their pharmacology. The formation of nitrosated esters of carvedilol is well within the technical grasp of one of ordinary skill in the art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Based on the disclosure of '538 one of ordinary skill in the art would know that modifying carvedilol by adding a nitrosated ester would predictably form the alpha adrenergic receptor antagonist that releases nitric oxide. Although the '538 disclosure does not specifically teach the hexanoic ester, it does teach the genus which includes the specific derivative. Furthermore, optimization of esters used in this manner to vary the alkyl chain length would be considered routine in the art.

The Supreme Court stated in *KSR* "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual

application is beyond that person's skill." *KSR Intern. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731 (2007).

Similarly, the teaching of '538 teaches specific examples of improving closely related compounds by forming the nitrosated ester; therefore, one of ordinary skill in the art would recognize that the same modification could be used to improve carvedilol. Furthermore, '538 specifically suggests this type of modification. Therefore, one of ordinary skill in the art would predictably arrive at the claimed invention. Therefore, **the claims are rejected**.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 36, and 57-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds identified as having activity, does not reasonably provide enablement for the claimed utility of the entirety of the claim scope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of affecting NO concentration in vivo.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Nature of Invention. The nature of the invention involves pharmaceutical compounds derivatized with NOx.

Scope of the Invention. The scope of the invention is for a genus of compounds of formula I with in excess of millions of species encompassed by the various alternative definitions of Y.

State of the Art and Level of Skill in the Art. Although the level of skill in the art is very high, using pharmaceuticals to treat patients is a highly unpredictable art. Yamamoto et al. (Yamamoto et al., Exper. Biol. and Medicine, 225 (3): 200. (2000)) teaches that the amount of NO released determines the pharmacological properties of the drugs which can have adverse side effects and can activate a cascade of cellular processes.

Number of Working Examples and Guidance Provided by Applicant. The applicant provides table I showing activity values for 4 compounds within the claim scope.

Unpredictability of the Art and Amount of Experimentation. The art of using pharmaceuticals to treat patients is highly unpredictable for many reasons including the inability to predict the amount of NO a given pharmaceutical agent will release. Because the amount and duration of NO release is determined by the particular structure of the pharmaceutical one of ordinary skill in the art would not know which derivatives would be effective unless there is a reasonable correlation between the types of derivatives and their affect on a model biological system. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would have the desired effect. When small variations in structure such as the addition of a methyl group can have significant effects on the pharmacology, without specific guidance or correlations indicating how the structure of species affects its ability to create the desired effect, the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the millions of compounds within the claimed scope.

Considering the above factors, the claims are clearly not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

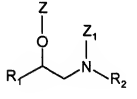
10. Claims 1 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims define a variable using terminology that one of ordinary skill in the art would not understand what constitutes the metes and bounds of the claims. Specifically, the claims use the phrase "group capable of binding Y" without providing a definition in the specification. "Binding" a variable group such as

Y does not have a clear meaning in the art in this context. Appropriate correction is required.

11. Claims 1, 36, 57-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims first refer to formula (I):

$$A\text{-}(Y\text{-}ONO_2)_s \text{ (I)}$$

then a formula (II):



however, it is not clear where the (Y-ONO2)s groups are attached on the "A" structure of formula (II). One of ordinary skill in the art would not know whether the (Y-ONO2)s were allowed to be attached to any part of the "A" structure or whether they were only permitted at the Z or Z1 positions. The examiner recommends combining formula (I) and (II) to remove the ambiguity as to the bonding positions.

Conclusion

The claims are not in condition for allowance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Havlin whose telephone number is (571) 272-9066. The examiner can normally be reached on Mon. - Fri., 7:30am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful the examiner's supervisor, Joe McKane can be reached at (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Robert Havlin/
Examiner, Art Unit 1626